UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/599,997	06/23/2000	IMRE KOVESDI	204526	8984

23460 7590 10/22/2002

LEYDIG VOIT & MAYER, LTD
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6780

EXAMINER
MCKELVEY, TERRY ALAN

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/599,997	KOVESDI ET AL.	
	Examiner	Art Unit	
	Terry A. McKelvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-27* is/are pending in the application.

4a) Of the above claim(s) *16,17,22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-15,18-21 and 24-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Claims 16-17 and 22-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 6, filed 1/16/02.

This application contains claims 16-17 and 22-23 drawn to an invention nonelected with traverse in Paper No. 6. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 21, and 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bouck et al (U.S. Patent No. 6,288,024) in view of Cuthbertson (applicant reference AB). This rejection is maintained for reasons of record set forth in Paper No. 8, mailed 4/9/02, and repeated below. Applicants' arguments filed 7/9/02 have been fully considered but they are not deemed to be persuasive.

Bouck et al a method of inhibiting angiogenesis within a tissue by providing exogenous SLED to cells associated with the tissue. SLED is defined as including any antiangiogenic derivative of PEDF (column 3), which encompass both PEDF and therapeutic fragments thereof. This reference teaches that in

one application, the tissue can be eye tissue, in which case the presence of exogenous SLED will inhibit novel angiogenesis associated with a variety of disorders of the eye (column 4). It is taught that within the context of the inventive method, SLED can be supplied alone or in conjunction with other known angiogenic factors, including dominant negative receptors for known inducers of angiogenesis, and that employing SLED in combination with other antiangiogenic agents can potentiate a more potent (and potentially synergistic) inhibition of angiogenesis within the desired tissue (column 5). This reference teaches that SLED polypeptide can be provided to the tissue of interest by transferring an expression cassette including a nucleic acid encoding SLED to cells associated with the tissue of interest (column 6). The promoter that drives the expression of SLED is taught as being any appropriate promoter for use, including a CMV promoter, and that any suitable vector can be employed, such as adenoviral vectors (column 6).

Bouck et al do not specifically teach an adenoviral vector comprising a nucleic acid encoding PEDF or therapeutic fragment thereof, which can be used for a specific purpose, such as treatment of an eye disease.

Cuthbertson teach a method for generating a genetically-engineered in situ ocular cell, comprising contacting an ocular

cell with an adenovirus vector (throughout reference; claim 3). This reference teaches that the method can be used to treat a wide variety of conditions and diseases (column 5).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an adenovirus vector comprising a nucleic acid encoding PEDF or therapeutic fragment of PEDF or further comprising a nucleic acid sequence encoding other therapeutic substances such as other antiangiogenic substances, because Bouck et al teach that such vectors can be used to provide SLED to cells associated with the tissue of interest, that SLED will inhibit novel angiogenesis associated with a variety of eye disorders, including some which are specifically mentioned by Cuthbertson, and Cuthbertson teaches that eye diseases can be treated with adenoviral vectors expressing and exogenous gene.

One would have been motivated to do so for the expected benefit of making an adenoviral vector useful for treating a variety of eye diseases as taught by Bouck et al and Cuthbertson et al. Absent evidence to the contrary and based upon the teachings of the cited references, there would have been a reasonable expectation of success in making the claimed adenoviral vector.

Regarding the use of a gene encoding soluble VEGF receptor in the adenoviral vector, it would have been obvious to use any of the antiangiogenic genes that are and were well known in the art, including one encoding soluble VEGF receptor, because Bouck et al teach to further include other known angiogenic factors, including dominant negative receptors for known inducers of angiogenesis, which encompasses soluble VEGF receptor.

Regarding the use of linking the therapeutic substance other than PEDF or therapeutic fragment thereof, to an ER localization signal peptide, it would have been obvious to do so because it is and was well known to do so in order to provide for the export of the substance, in order to enhance its therapeutic effect.

Response to Arguments

The applicant separates the arguments based upon the references, not the individual rejections. Each argument is addressed below according to the first rejection in which that reference appears.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on

combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The applicant argues that the Bouck '024 patent does not describe an adenoviral vector comprising a nucleic acid encoding PEDF. The applicant admits that this reference mentions use of an adenoviral vector, but argues that it does not demonstrate the use of such an adenoviral vector and gives no guidance as to the desirable characteristics for the development of a suitable vector, and thus provides no reasonable expectation of success for use of the vector to administer the vector. This argument is not persuasive because this reference was not relied upon exclusively for the teachings of adenoviral administration of a nucleic acid. The rejection was based upon the combination of the cited references. Cuthbertson, not Bouck '024, was relied upon for the teachings of a method for delivering a nucleic acid in situ to ocular cells, comprising contacting an ocular cell with an adenovirus vector. This reference teaches that the method can be used to treat a wide variety of conditions and diseases, which encompasses treatment of an eye disease which is based upon administration of PEDF nucleic acid. The reasonable expectation of success comes from the combination of the cited teachings and the high level of skill in the art that would enable one of

ordinary skill in the art to apply the adenoviral nucleic acid administration to in situ ocular cells teachings of Cuthbertson to performing the method taught by Bouck '024 which specifically suggests that adenovirus can be used to administer a PEDF nucleic acid. The applicant argues that Cuthbertson does not teach anything about PEDF nucleic acid in an adenovirus vector. This argument is not persuasive for the same basic reason described above, this reference was not relied upon for this teaching, Bouck '024 was. The applicant did not address the obviousness of the combination of the teachings at all.

The applicant argues that neither Bouck '024 nor Cuthbertson teach an adenoviral vector comprising a nucleic acid encoding both PEDF and another anti-angiogenic substance. This argument is not persuasive because the obviousness of the claims that have this further limitation is based upon the combination of the teachings of the cited references. Bouck '024 teach that within the context of the inventive method, SLED can be supplied alone or in conjunction with other known angiogenic factors, including dominant negative receptors for known inducers of angiogenesis, and that employing SLED in combination with other antiangiogenic agents can potentiate a more potent (and potentially synergistic) inhibition of angiogenesis within the desired tissue (column 5). Thus, this reference specifically

suggests administration of PEDF with other antiangiogenic agents. Bouck '024 also teaches that PEDF can be administered by administering nucleic acid such as by using an adenovirus vector and that the vector can further include other genes that encode pharmacologically active proteins or substances (column 7) (which within the context of the teachings described within the Bouck '024 patent certainly encompasses antiangiogenic substances) and Cuthbertson teaches how to administer an adenovirus vector to deliver a nucleic acid to express an exogenous protein. Thus, it would have been obvious to include additional antangiogenic nucleic acids in the adenovirus vector made obvious from the teachings of the cited references.

The applicant argues that the Office Action does not point to anything within the Bouck '024 patent or the Cuthbertson patent that would lead one of ordinary skill to combine their disclosures and that even if combined, does not necessarily result in the claimed adenoviral vector. This argument is not persuasive because the applicant totally ignores the particulars set forth in the Office Action, including, for example, that Bouck specifically teaches use of adenovirus vector to administer PEDF nucleic acid and that Cuthbertson specifically teaches that the adenoviral vector administration of nucleic acid taught by the patent can be used to treat ocular disease,

which is what Bouck '024 specifically teaches is the purpose of PEDF nucleic administration. These are very strong teachings to combine each other. There is no requirement that the teachings have to point to each other by name, which is what the applicant appears to be arguing. The obviousness of the combination of the references to result in the claimed invention was set forth in the previous Office Action, and the actual basis of that obviousness was not truly addressed by the applicant. For these reasons, the applicant's arguments are not persuasive in overcoming the instant rejection, and the rejection remains for reasons of record.

Claims 1, 3-15, 21, and 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bouck et al (U.S. Patent No. 6,288,024) and Cuthbertson (applicant reference AB) as applied to claims 1, 21, and 24-27 above, and further in view of Brough et al (U.S. Patent No. 6,113,913) and Brough et al' (U.S. Patent No. 6,225,113). This rejection is maintained for reasons of record set forth in Paper No. 8, mailed 4/9/02, and repeated below. Applicants' arguments filed 7/9/02 have been fully considered but they are not deemed to be persuasive.

The teachings of Bouck et al and Cuthbertson are cited above and applied as before.

Bouck et al and Cuthbertson do not specifically teach particular types of replication defective adenoviral vectors or the adenoviral vectors further comprising a cis-acting factor such as MAR or LCR, or adenoviral vectors further comprising a nucleic acid encoding a transacting factor such as HSV ICP0.

Brough et al ('913) teach recombinant adenoviral vectors being deficient in E1A or E1B in combination with a deficiency in E2 and/or E3 and/or E4 (throughout the reference; column 5). This reference teaches that deficient adenoviruses have been engineered to reduce deleterious effects and that the deficient adenoviral vectors will find applications in treating diseases through the transfer of therapeutic genes (columns 2 and 4).

Brough et al ('113) teach a recombinant adenoviral vector deficient in the E4 gene comprising a gene encoding a trans-acting factor such as HSV ICP0, which can further comprise a cis-acting factor such as MAR or LCR (column 4). It is taught that the vector can be deficient in other regions (column 6). These vectors are taught as providing a method of modulating the persistence of expression of a trans gene in a cell (abstract; throughout the reference).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the adenoviral vector made from the combined teachings of Bouck et al and

Cuthbertson because both Brough et al references teach that it is within the ordinary skill in the art to make replication defective adenoviral vectors and defective adenoviral vectors further comprising a gene encoding a trans-acting factor like HSV ICP0, and cis-acting factors such as MAR and LCR.

One would have been motivated to do so for the expected benefit of making a replication defective adenovirus vector that has reduced deleterious effects and which provides a method of modulating the persistence of expression of the trans gene, as taught by Brough et al and Brough et al, for the adenoviral vectors made obvious from the combined teachings of Bouck et al and Cuthbertson. Absent evidence to the contrary and based upon the teachings of the cited references, there would have been a reasonable expectation of success in making the claimed adenoviral vector.

Response to Arguments

The applicant argues that "The Office Action, appreciating the deficiencies of the Bouck '024 patent and the Cuthbertson '702 patent, relies on the Brough '913 patent and the Brough '113 patent to cure the substantial defects in the combination of the Bouck '024 patent with the Cuthbertson '702 patent." This is a misrepresentation of the rejection based upon the

combination of the four references. This rejection was made to reject claims with additional limitations, i.e., claims 3-15, based upon the obviousness of the combination of the four references. It was not done to "cure the substantial defects in the combination of the Bouck '024 patent with the Cuthbertson patent". The claims that are rejected in both rejections (claims 1, 21, and 24-27) were included in the four reference rejection because they are covered by the rejection, not because the teachings of all four references need to be combined to demonstrate the obviousness of the claimed inventions of those particular claims. It is Office policy to include these claims in any rejections which add additional references to address the limitations of other claims (claims 3-15 in the instant case) not covered by the first rejection.

The applicant attacks the Brough references individually for what they do not teach, even though the rejection is based upon the obviousness of the combination of the cited references, and that these references were relied upon for specific teachings not addressed by the applicant's arguments. This argument is not persuasive for the same reasons described above. The applicant ignores the actual basis of the obviousness of the combination of the four references, including the particular teachings in the two Brough references which makes obvious to

one of ordinary skill in the art to combine all of the cited teachings. Therefore, the applicant arguments are not persuasive in overcoming the instant rejection, and the rejection remains for reasons of record.

Claims 1, 18-21, and 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bouck et al (U.S. Patent No. 6,288,024) and Cuthbertson (applicant reference AB) as applied to claims 1, 21, and 24-27 above, and further in view of Wickham et al (U.S. Patent No. 5,962,311). This rejection is maintained for reasons of record set forth in Paper No. 8, mailed 4/9/02, and repeated below. Applicants' arguments filed 7/9/02 have been fully considered but they are not deemed to be persuasive.

The teachings of Bouck et al and Cuthbertson are cited above and applied as before.

Bouck et al and Cuthbertson do not specifically teach the adenoviral vector comprising a chimeric coat protein (which comprises a nonnative amino acid sequence) which directs entry into cells of the vector that is more efficient than wild type, which efficiently binds to a broader range of cells, and which binds an endogenous binding site not recognized by the wild type.

Wickham et al teach adenoviral vectors comprising a chimeric adenovirus fiber (which is a modified coat protein) (abstract; throughout the reference). This reference teaches that adenoviral vectors are preferred over other gene therapy vectors and that a drawback of the vectors in gene therapy is that all cells that comprise receptors for the adenoviral fiber and penton base will internalize the adenovirus and consequently the genes being administered, not just the cells in need of therapeutic treatment (column 3). Wickham et al teach that limiting adenoviral entry to specific cells and/or expanding the repertoire of cells amenable to adenovirus-mediated gene therapy constitutes a substantial improvement over current technology (columns 3-4). This reference teaches how to accomplish this, through the modification of the adenoviral fiber by incorporation of non-native sequences for a ligand to a cell surface receptor (columns 4-5). Wickham et al teach that the method can be carried out to introduce adenovirus into any cell, even a cell that wild-type adenovirus binds and enters with relatively high efficiency (column 20).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the adenoviral vector made from the combined teachings of Bouck et al and Cuthbertson by making the vectors comprise a chimeric adenovirus

fiber because Wickham et al teach that it is within the ordinary skill in the art to make adenoviral vectors further comprising a chimeric coat protein having an inserted non-native sequence which directs the entry of the adenovirus to particular cells.

One would have been motivated to do so for the expected benefit of making an adenovirus vector that has limited adenoviral vector entry and/or expanded range of cells that can be entered by the adenovirus, useful for more directly targeting the adenovirus to the cells in need of therapeutic treatment, overcoming a drawback of adenovirus for gene therapy, as taught by Wickham et al, for the adenoviral vectors made obvious from the combined teachings of Bouck et al and Cuthbertson. Absent evidence to the contrary and based upon the teachings of the cited references, there would have been a reasonable expectation of success in making the claimed adenoviral vector.

Response to Arguments

The applicant argues that the Office Action relies upon the Wickham patent as a cure for the defective Bouck and Cuthbertson patent combination. This is a similar misrepresentation as described above for the four reference rejection. The same type of nonpersuasive argument is applied to the Wickham reference, arguing what the reference does not teach, without addressing

the basis of the obviousness rejection which relies upon a different teaching of Wickham not addressed by the applicant which makes obvious to one of ordinary skill in the art to combine all of the cited teachings. For the same reasons described above, the applicant's arguments are not persuasive and the rejection remains for reasons of record.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning missing attachments or other minor formalities of this communication should be directed to the patent analyst, Zeta Adams, whose telephone number is (703) 305-3291.

Any inquiry concerning rejections or other major issues in this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 7:30 AM to about 6:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, can be reached at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

October 19, 2002